Post-radiation change in MRI Dynamic Contrast Enhanced Ktrans did not explain tumor reoxygenation of irradiated naturally-occurring canine tumors.

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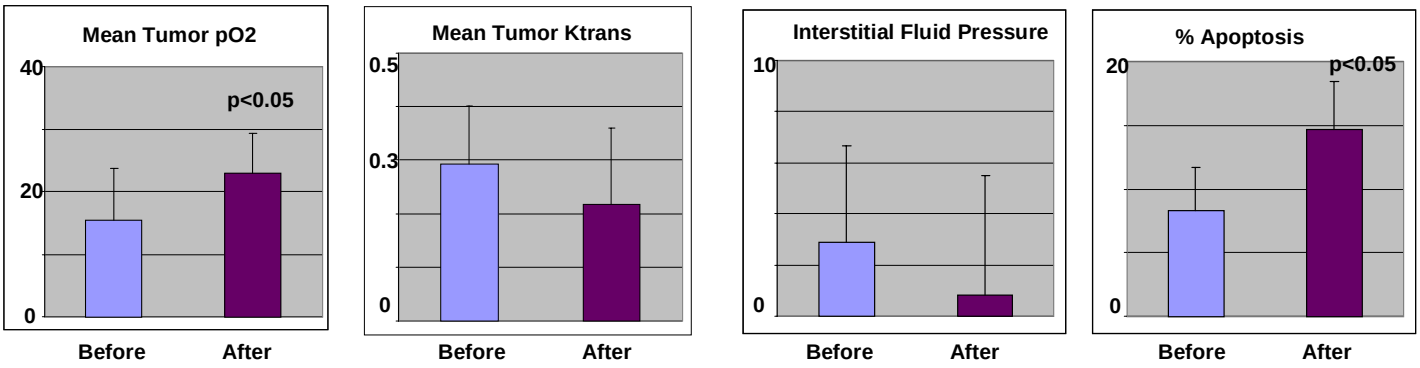
Introduction/Purpose: Exploitation of radiation-induced reoxygenation could impact cancer patient survival, but the mechanisms of this process remain unclear [1]. In this study we evaluated changes in dynamic contrast enhancement (DCE) with magnetic resonance imaging (MRI) before and after a single initial dose of radiation. We related those changes to tumor oxygen levels, microvascular perfusion (MVP) and density (MVD), apoptosis and interstitial fluid pressure (IFP) to investigate mechanisms involved in reoxygenation. Most studies using DCE-MRI to evaluate radiation effects are done after full course radiation [2-5]. In our study we looked at the changes induced by a single fraction of radiation before substantial repopulation, reassortment and repair could take place. We hypothesized that reoxygenation of tumors after radiation was due to reperfusion of collapsed vessels after apoptotic cell death and decreased interstitial fluid pressure [5], and that reperfusion would be reflected as an increase in Ktrans as measured by DCE.
Methods: DCE-MRI was performed on 9 dogs with naturally-occurring malignant tumors using a 1.5 GE Signa LX 9.1 MRI instrument before and 24 hours after an initial 3 Gy fractionated dose of radiation (Siemens 6 MV linear accelerator). DCE-MRI of whole tumors was done using T1 fast spin echo sequence with 30-35 second phases during and after IV injection of gadolinium DTPA (0.1 mmol/kg, Magnevist). After each MRI-DCE, pO2 and MVP were measured by Oxford Optronix OxyLite/OxyFlow and IFP by wick-in-needle methods. Percent apoptosis and MVD were quantified from tumor biopsies. DCE-MRI analysis was done by region-of-interest analysis of the entire tumor volume using 3D geometrically constrained region growth and an automated arterial input function (3D GEORG) (Perfusion Analyzer, VirtualScopics Inc., Rochester NY). The input transfer rate constant (Ktrans) was derived by "intensity based" two compartment modeling [6]. Pre- and post-radiation DCE data were statistically evaluated for differences by Shapiro-Wilk test for normality p-value, paired/signed t-tests and Pearson and Spearman correlation coefficient analysis.
Results: There were 5 soft tissue sarcomas, 2 carcinomas,1 multilobular osteochondrosarcoma, and 1 mast cell tumor. One dog's DCE-MRI data was excluded due to excess motion artifact. Four of the tumors were hypoxic prior to radiation, with median pO2 values < 10 mm Hg. All hypoxic tumors became normoxic after the 3 Gy fraction, with statistical increase in mean/median pO2 and decreased hypoxic fraction, whereas Ktrans decreased in 6/8 dog tumors. Apoptosis increased in all 9 tumors and interstitial fluid pressure decreased in 8/9 tumors.



Conclusions: Dogs with naturally-occurring tumors make an excellent translational model because imaging, medical and surgical procedures are similar to those used in people and yet, more intensive sampling and invasive procedures are feasible for biologically-realistic physiological correlation. Ktrans decreased consistently after radiation, even in the presence of decreased interstitial fluid pressures and increased apoptosis, so improved vascular delivery did not explain the concurrent reoxygenation of tumors. Ktrans depends not only upon vascular perfusion but also on vessel permeability, IFP and interstitial fluid volume. The decreased Ktrans most likely was due to decreased vascular permeability and/or surface area secondary to radiation-induced endothelial cell swelling. Since there was a lack of evidence of increased perfusion after radiation, we propose that the reoxygenation in these tumors was due to decreased cell consumption. DCE was a convenient, noninvasive and more consistent *in vivo* indicator of overall vascular delivery. In comparison, directly- measured microvascular perfusion results were more variable and also more difficult to interpret.

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